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From: Born, Michael
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Thank you

L1 ANSWER 1 OF 3 USPATFULL
AN 86:34823 USPATFULL
TI Octahydroindolizinepropanoic acids and related compounds as enzyme inhibitors
IN Mylderse, Jon S., Indianapolis, IN, United States
Patchett, David S., Brownsburg, IN, United States
PA Eli Lilly Company, Indianapolis, IN, United States (U.S. corporation)
PI US 4594431 19860610
AI US 1983-[illegible] 19830[illegible]
DT Utility
EXNAM Primary Examiner: Brust, Joseph Paul
LREP Scanlon, William B.; Whale, Arthur P.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 991
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4594431 19860610
AB Octahydro-5-oxoindolizine-6-propanoic acids and octahydro-6-oxopyrido[1,2-A]pyridine-7-propanoic acids, the decarboxy and related ester and perhydro derivatives thereof inhibit angiotensin I converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are O-acyl and O-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A and B via hydrogenolysis.
SUMM The **ACE inhibitors** known as A58365 factor A and A58365 factor B represented by the following structural formulae ##STR1## produced by culturing Streptomyces chromofuscus NRRL 15194 are hydrogenated to the corresponding perhydro derivatives, 3-carboxyoctahydro-5-oxo-6-indolizinepropanoic acids and 4-carboxyoctahydro-6-oxo-7-pyrido[1,2-a]pyridinepropanoic acids, and the deoxy and decarboxy hydrogenolysis products, and the perhydro products of the latter. The hydrogenation and hydrogenolysis products obtained are useful hypotensive agents, in particular deoxy factor A obtained by hydrogenolysis of factor A. Certain acyl and sulfonyl derivatives of A58365 factors A and B are also provided as intermediates to deoxy factor A and deoxy factor B.

SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated with test compounds.

SUMM The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in hypertensive mammals. The compounds or the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about [illegible] and about [illegible] mg. For parenteral administration, the [illegible] salt or biologically cleavable ester is dissolved or suspended in [illegible]

physiologically acceptable fluid for injection, either intramuscularly or intravenously. Suitable fluids or diluents such as Water-For-Injection, 0.9% saline, 5% glucose or other fluid may be used. For oral administration the compound or a salt or ester thereof may be formulated in gelatin capsules, tablets or liquid suspensions. The administration can be carried out with a single daily dose or multiple daily doses.

SUM3 Preferred **ACE inhibitors** are represented by the formula 1 wherein R and R.sub.1 are hydrogen, n is 1 or 2 and Y is .dbd.CH--CH.dbd..

SUM4 The compounds of the formula 4 are useful intermediates for preparing the **ACE inhibitors** deoxy factor A and deoxy factor B represented by the formulae 1e and 1f. In addition to their use as intermediates, the compounds represented by the formula 4 wherein R.sub.4 is a C.sub.2 -C.sub.6 alkanoyloxy group and the pharmaceutically acceptable salts thereof are also active **ACE inhibitors**. In particular, a preferred acyl derivative is the O-acetyl factor A which has demonstrated ACE inhibition activity in the same tests in which factor A and the reduction products of factors A and B of formula 1 demonstrated activity. Accordingly, the O-acyl derivatives of the formula 4 and the pharmaceutically acceptable, non-toxic salts and biologically active esters thereof are useful hypotensive agents in the treatment of hypertension.

SUM5 The A58365 factors A and B (formula 3) which are used as starting materials for preparing the **ACE inhibitors** of this invention are obtained by culturing a new strain of Streptomyces chromofuscus NRRL 15098 as described in co-pending applications serial Nos. 409,765 now U.S. Pat. No. 4,404,281 and 409,764 now U.S. Pat. No. 4,404,282, filed Aug. 19, 1982. The compound of the formula 3 wherein n is 1 is designated in the co-pending application as A58365 factor A, while the compound of the formula 3 wherein n is 2 is designated as A58365 factor B. As described in the co-pending applications, the compounds of the formula 3 are prepared by culturing Streptomyces chromofuscus NRRL 15098 under aerobic fermentation conditions in an aqueous nutrient culture medium containing assimilable sources of carbon, inorganic salts and nitrogen. The culture medium employed in the fermentation can be any one of a number of media since the microorganism is capable of utilizing energy from a variety of nutrient sources. For example, a variety of carbonydrates including sugars and starches can be included in the culture medium to supply the carbon requirements of the microorganism. Likewise, various sources of nitrogen such as the amino acids, distillers extracts, meat peptones, and casein hydrolysates can be employed in the culture medium. In the interest of economy in production, optimal yield, and ease of isolation of the ACE factors, certain culture media are preferred. For example, one of the preferred sources of carbon is potato dextrin, although various sugars such as glucose or fructose may also be used. Preferred sources of nitrogen are

peptones and the hydrolysates of casein. As is common in the fermentation of microorganisms, nutrient inorganic salts can be incorporated in the culture medium for the production of the ACE factors. Such inorganic salts are the customary salts capable of yielding sodium, potassium, ammonium, calcium, phosphate, chlorine, carbonate, and like ions. Trace elements may also be added to the fermentation medium; however, these are commonly added in sufficient trace amounts as constituents of other ingredients added to the media.

[illegible] The microorganism employed in the method for producing the **ACE inhibitors** of this invention has been identified as a new strain of Streptomyces chromofuscus (Preobrashenskaya, Blinov and Ryabova 1957), Pridham, Hessetine and Benedict, "A Guide for the Classification of Streptomycetes According to Selected Groups", Appl. Microbiol. 6:52-59, (1957).

L1 ANSWER 2 OF 3 USPATFULL
AN 86:23431 USPATFULL
TI Method of treating heart failure and medicaments therefor
IN Steffen, Robert P., Saline, MI, United States
Evans, Dale B., Saline, MI, United States
Kaplan, Harvey R., Ann Arbor, MI, United States
Weisbach, Jerry A., Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States U.S. corporation
PI US 4584299 19860422
AI US 1984-612275 19840521 (6)
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.
LREP Thierstein, Joan
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 548
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4584299 19860422
AB Method for treating heart failure by increasing myocardial contractility and cardiac output with the administration of a pharmaceutical composition containing a combination of active ingredients including a pyridazinone or pyridin-one cardiotonic agent and a tetrahydroisoquinoline-3-carboxylic or octahydro-1H-indole-2-carboxylic acid **ACE inhibitor**.

SUMM Antihypertensive agents which attribute their activity to inhibition of angiotensin-converting enzyme (**ACE inhibitors**) have been described. For example, aryl derivatives of 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acids are described in U.S. Pat. No. 4,344,949 and acylated octahydro-1H-indole-2-carboxylic acids are described in U.S. Pat. No. 4,425,355.

SUMM Combinations of antihypertensive agents and diuretics are well-known in the art. ACE-inhibiting antihypertensive agents have also been reported to be useful in combination with diuretic compounds in U.S. Pat. No. 4,217,347. Combinations of **ACE inhibitors** with diuretics, saluretics, .alpha.-adrenolytics, .beta.-blockers, calcium antagonists or vascular dopaminergic receptor agonists are reported in European Patent Publications 51,020, 69,946, and 49,658.

SUMM The present invention relates to a combination of certain **ACE-inhibitors** with certain cardiotonic agents resulting in a synergistic increase in myocardial contractility and cardiac output thereby rendering such combinations useful in treating heart failure.

SUMM The compounds of formulae I and II have been reported as cardiotonic agents and their effectiveness demonstrated in standard pharmacological test procedures, for example, in causing a significant increase in the myocardial contractility in the pentobarbital anesthetized dog with low

or minimal changes in heart rate and **blood pressure**, see U.S. Pat. No. 4,353,905 and U.S. application Ser. No. 515,[illegible] of July 22, 1983.

SUM1 This invention relates to the discovery that the combination of a cardiotonic agent as defined above with an **ACE inhibitor** as defined above results in a synergistic increase in myocardial contractility and cardiac output and therefore may be used in pharmaceutical compositions for treating heart failure.

SUM2 The **ACE inhibitor** components in the combination have asymmetric carbon atoms. The compounds accordingly exist as optical isomers and diastereomers or as racemates and mixtures thereof. All of these are within the scope of the invention. The 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid used in this invention has the L configuration. This configuration has been shown to be required for biological activity, and thus **ACE inhibitors** of the invention are derived from either L(--) or DL-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

SUM3 The antihypertensive **ACE inhibitors** can be produced as described in U.S. Pat. No. 4,344,949 for the isoquinoline-3-carboxylic acids and in U.S. Pat. No. 4,425,355 for the octahydro-indole-2-carboxylic acids. According to this invention, a combination of a cardiotonic compound and an **ACE inhibitor** is administered in an effective amount which comprises a total daily dosage of about 1 to 200 mg, preferably 1 to 20 mg of cardiotonic agent and about 1 to 100 mg, preferably 1 to 20 mg of the **ACE inhibitor** to a subject, e.g., a mammalian species, suffering from heart failure. Such total daily dosages can be used in a single administration of the total amount or in divided doses two to four times daily. Generally, once or twice daily is preferred. This preferred dosage is about 3 to 60 mg of cardiotonic agent and about 3 to 60 mg of the **ACE inhibitor** once daily or about 1 to 20 mg of cardiotonic and about 1 to 20 mg of **ACE inhibitor** twice daily. The preferred route of administration is oral.

SUM4 The pharmaceutical compositions of the invention can take any of a wide variety of oral and parenteral dosage forms. The dosage forms comprise as the active components, a cardiotonic compound as defined previously and an **ACE inhibitor** as defined previously as free bases and free acids thereof or as corresponding pharmaceutically acceptable salts.

EXP1 Barbiturate anesthetized, vagotomized dogs were mechanically respired with room air. Arterial **blood pressure** and heart rate were recorded continuously. A series of [illegible] including angiotensin I and angiotensin II, each of which produced characteristic and reproducible **blood pressure** and

heart rate responses, was administered before and after rising intravenous doses of 0.03, 0.3, and 3.0 mg/kg of B.

DETD Compound B had no effect on **blood pressure** or heart rate at the doses tested. Compound B selectively inhibited the vasopressor response to angiotensin I while having no significant effect on angiotensin II (Table 1).

DETD TABLE 1

Effects of 2-[2-(1-carboxy-3-phenylpropyl-amino)-1-oxopropyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (B) on Angiotensin I and Angiotensin II Pressor Response in Anesthetized Dogs (N = 2)

B, mg/kg IV	Mean **Blood Pressure** Change, mm Hg: Angiotensin I	Angiotensin II
Control.sup.a	51 .+-. 14	53 .+-. 15
.03	43 .+-. 21	58 .+-. 16
.3	8 .+-. 3	66 .+-. 14
3.0	3 .+-. 3	72 .+-. 14

.sup.a Control mean **blood pressure** was 135 .+-. 8 mm Hg

DETD Adult mongrel dogs of either sex were anesthetized with sodium pentobarbital and ventilated artificially with a positive pressure respirator. Anesthesia was maintained by a continuous infusion of pentobarbital. Arterial **blood pressure**, left intraventricular pressure, and its first derivative dP/dt (an index of myocardial contractility), and heart rate were recorded continuously. Cardiac output, measured by thermodilution, was recorded before myocardial depression, when stable myocardial depression was achieved (approximately 30 minutes), and ten minutes following each dosage. Following surgical preparation animals were allowed 30 minutes to stabilize hemodynamically prior to induction of myocardial depression. Myocardial depression was induced and maintained by administration of dl-propranolol at 4 mg/kg IV bolus and continuous infusion of 0.125 mg/kg/min. Once stable depression was achieved, animals received either (a) B at 0.3 mg/kg followed by A in rising doses from 0.01 to 1.0 mg/kg, n=6, (b) saline followed by A 0.01 to 1.0 mg/kg, n=6. Each agent was given as an IV bolus. Cardiodynamic and hemodynamic measurements were taken prior to, following stable myocardial depression, and ten minutes following each bolus injection. Ten minutes were sufficient to achieve stable response to each dose.

L2 ANSWER 3 OF 3 USPATFULL
AN 86:1663 USPATFULL
TI Phenazine **ACE inhibitor** produced from streptomyces species
IN Bush, Karen, Kingston, NJ, United States
Slusarchyk, Dorothy S., Belle Mead, NJ, United States
Liu, Wen-Chih, Princeton Junction, NJ, United States
PA E. R. Squibb & Sons, Inc., Princeton, NJ, United States (U.S. corporation)
PI US 4569675 19860204
AI US 1983-562914 19831219 (6)
DT Utility
EXNAM Primary Examiner: Berch, Mark L.
LREP Levinson, Lawrence S.; Barrack, Donald J.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1,2
DRWN No Drawings
LN.CNT 350
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Phenazine **ACE inhibitor** produced from streptomyces species
PI US 4569675 19860204 <--
ABEX EM5523 has been analyzed and found to be 3,6-dihydroxyphenazine-1-carboxylic acid, a compound having the formula ##STR1## EM5523, and pharmaceutically acceptable salts thereof, are hypotensive agents. They inhibit the conversion of the decapeptide angiotensin I to angiotensin II and, therefore, are useful in reducing or relieving angiotensin related hypertension. The action of the enzyme renin on angiotensinogen, a pseudoglobulin in blood plasma, produces angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II. The latter is an active pressor substance which has been implicated as the causative agent in several forms of hypertension in various mammalian species, e.g., humans. EM5523 intervenes in the angiotensinogen.fwdarw.(renin).fwdarw.angiotensin I.fwdarw.(ACE).fwdarw.angiotensin II sequence by inhibiting angiotensin converting enzyme and reducing or eliminating the formation of the pressor substance angiotensin II. Thus by the administration of a composition containing one (or a combination) of the compounds of this invention, angiotensin dependent hypertension in a species of mammal (e.g., humans) suffering therefrom is alleviated. A single dose, or preferably two to four divided daily doses, provided on a basis of about 1.1 to 100 milligrams per kilogram of body weight per day, preferably about 1 to 15 milligrams per kilogram of body weight per day, is appropriate to reduce **blood pressure**. The substance is administered parenterally.

CLM What is claimed is:
2. A method of lowering **blood pressure** in a mammal in need thereof, which comprises administering to said mammal an effective amount of 3,6-dihydroxyphenazine-1-carboxylic acid, or a

pharmaceutically acceptable basic salt thereof.

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HIGHEST PATENT NUMBER: US6[illegible]
CA INDEXING IS CURRENT THROUGH 22 Feb [illegible] UPCA
ISSUE CLASS FIELDS (INCL) CURRENT THROUGH: 22 Feb [illegible]
REVISED CLASS FIELDS (NCL) LAST RELOADED: Oct 1999
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Nov 1999

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>>> /IC5, and /IC (/IC6) fields, respectively.  The thesauri in      <<<
>>> the /IC5 and /IC fields include the corresponding catchword      <<<
>>> terms from the IPC subject headings and subheadings.             <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s (ace inhibitor#)/ti,ab,clm

            73 ACE/TI
             1 ACES/TI
            74 ACE/TI
                 ((ACE OR ACES)/TI)
          5286 INHIBITOR#/TI
            34 (ACE INHIBITOR#)/TI
                 ((ACE(W)INHIBITOR#)/TI)
           245 ACE/AB
            48 ACES/AB
           287 ACE/AB
                 ((ACE OR ACES)/AB)
         11779 INHIBITOR#/AB
           107 (ACE INHIBITOR#)/AB
                 ((ACE(W)INHIBITOR#)/AB)
           376 ACE/CLM
           141 ACES/CLM
           496 ACE/CLM
                 ((ACE OR ACES)/CLM)
         11816 INHIBITOR#/CLM
            85 (ACE INHIBITOR#)/CLM
                 ((ACE(W)INHIBITOR#)/CLM)
L1         171 (ACE INHIBITOR#)/TI,AB,CLM

=> d kwic


L1   ANSWER 1 OF 171  USPATFULL
AB       . . . catalytic reductive amination between ethyl
       2-oxo-4-phenylbutyrate and alanylproline using hydrogen, a catalyst and
       one or more additives to produce the ACE inhibitor,
       enalapril.
```

=> s l1 and blood pressure

[illegible] BLOOD
[illegible] BLOODS
[illegible] BLOOD
BLOOD OR BLOODS
[illegible] PRESSURE
[illegible] PRESSURES
[illegible] PRESSURE
PRESSURE OR PRESSURES
[illegible] BLOOD PRESSURE
BLOOD W PRESSURE
L3 [illegible] L1 AND BLOOD PRESSURE

=> d kwic 91

L2 ANSWER 91 OF 97 USPATFULL
AB . . . converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are O-acyl and O-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A. . .
SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated with test compounds.
SUMM The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in hypertensive mammals. The compounds or the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about 200 mg. and about 2,000 mg. For parenteral administration the compound or its salt or. . .

=> d bib, kwic 90-99

L2 ANSWER 90 OF 97 USPATFULL
AN 86:34323 USPATFULL
TI Octahydroindolizinepropanoic acids and related compounds as enzyme inhibitors
IN Mynderse, Jon S., Indianapolis, IN, United States
Fukuda, David S., Brownsburg, IN, United States
PA Eli Lilly Company, Indianapolis, IN, United States (U.S. corporation
PI US 4594431 19860610
AI US 1983-519360 19830801 (6
DT Utility
EXNAM Primary Examiner: Brust, Joseph Paul
LREP Scanlon, William B.; Whale, Arthur R.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 991
NO INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are O-acyl and O-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A. . .
SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated

with test compounds.

SUMM The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in pharmaceutically acceptable hypertensive mammals. The compounds of the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about 2[illegible] mg. and about 2,[illegible] mg. For parenteral administration the compound or its salt or. . .

L8 ANSWER 91 OF 97 USPATFULL
AN 86:23481 USPATFULL
TI Method of treating heart failure and medicaments therefor
IN Steffen, Robert P., Saline, MI, United States
Evans, Dale B., Saline, MI, United States
Kaplan, Harvey R., Ann Arbor, MI, United States
Weisbach, Jerry A., Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 4584299 19860422
AI US 1984-612275 19840521 (6
DT Utility
EXNAM Primary Examiner: Robinson, Douglas W.
LREP Thierstein, Joan
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 546
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . composition containing a combination of active ingredients including a pyridazinone or pyridin-one cardiotonic agent and a tetrahydroisoquinoline-3-carboxylic or octahydro-1H-indole-2-carboxylic acid **ACE inhibitor**.

SUMM . . . significant increase in the myocardial contractility in the pentobarbital anesthetized dog with low or minimal changes in heart rate and **blood pressure**, see U.S. Pat. No. 4,353,905 and U.S. application Ser. No. 513,799 of July 22, 1983.

DETD Barbiturate anesthetized, vagotomized dogs were mechanically respired with room air. Arterial **blood pressure** and heart rate were recorded continuously. A series of autonomic drug challenges including angiotensin I and angiotensin II, each of which produced characteristic and reproducible **blood pressure** and heart rate responses, was administered before and after rising intravenous doses of 0.03, 0.3, and 3.0 mg/kg of B. Compound B had no effect on **blood pressure** or heart rate at the doses tested. Compound B selectively inhibited the vasopressor response to angiotensin I while having no. . .

DETD TABLE 1

Effects of 2-[2-[(1-carboxy-3-phenylpropyl)-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (B) on Angiotensin I and Angiotensin II Pressor Response in Anesthetized Dogs (N = 2)

	Mean **Blood Pressure** Change (mm Hg)	
B, mg/kg IV	Angiotensin I	Angiotensin II
Control.sup.a	51 .+-. 14	53 .+-. 19
.03	43 .+-. 21	59 .+-. 16
.3	9 .+-. 3	66 .+-. 14
3.0	0 .+-. 0	72 .+-. 14

... control mean **blood pressure** was ... mm Hg
... . . . sodium ... barbital and ventilated artificially with a
positive pressure respirator. Anesthesia was maintained by ... of
infusion of pentobarbital. Arterial **blood pressure**,
left intraventricular pressure, and its first derivative as an index
of myocardial contractility , and heart rate were recorded ...
Cardiac. . .

L2 ANSWER 92 OF 97 USPATFULL
AN 86:66630 USPATFULL
TI Phenazine **ACE inhibitor** produced from streptomyces species
IN Bush, Karen, Kingston, NJ, United States
Slusarchyk, Dorothy S., Belle Mead, NJ, United States
Liu, Wen-Chih, Princeton Junction, NJ, United States
PA E. R. Squibb & Sons, Inc., Princeton, NJ, United States (U.S. corporation)
PI US 4568675 19860204
AI US 1983-562914 19831219 (6)
DT Utility
EXNAM Primary Examiner: Berch, Mark L.
LREP Levinson, Lawrence S.; Barrack, Ronald S.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1,2
DRWN No Drawings
LN.CNT 350
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Phenazine **ACE inhibitor** produced from streptomyces species
SUMM . . . weight per day, preferably about 1 to 15 milligrams per kilogram of body weight per day, is appropriate to reduce **blood pressure**. The substance is administered parenterally.
CLM What is claimed is:
2. A method of lowering **blood pressure** in a mammal in need thereof, which comprises administering to said mammal an effective amount of 3,6-dihydroxyphenazine-1-carboxylic acid, or a . .
.

L2 ANSWER 93 OF 97 USPATFULL
AN 85:72392 USPATFULL
TI Cardiovascular composition
IN Chan, Chi-Chung, Kirkland, Canada
Ford-Hutchinson, Anthony W., Beaconsfield, Canada
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 4558037 19851210
AI US 1984-617293 19840604 (6)
DT Utility
EXNAM Primary Examiner: Phillips, Delbert R.
LREP Mitri, Salvatore C.; Sudol, Michael C.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 886
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . cardiovascular composition is disclosed which comprises either dibenzo-thiepin derivatives alone or the combination of dibenzo-thiepin derivatives and angiotensin converting enzyme **ACE** **inhibitors**. These compositions represent a novel therapeutic approach to thromboembolic disease in man.
DETN . . . 15 minutes later by the second stimulation. Hexamethonium and hydralazine were co-administered in order to induce a drop in systemic **blood pressure** without a reflex increase in heart

rate.

HDTI Because it has been reported that Enalapril lowers **blood pressure** in several animal models of experimental hypertension [C. S. Sweet et al., Fed. Proc., 42, 167-17 . 198 and C. S. . . . . Pharmacol., 76, 167-176 1981], it was necessary to examine in separate experiments whether Enalapril and HDTI produced effects upon **blood pressure** and heart rate in this model. In particular, it was important to determine whether the cardiovascular effects of the HDTI Enalapril. . . . For the observed changes in platelet accumulation. As shown in Table II below, a combination of HD.. and Enalapril decreased **blood pressure** a reduction of 14.+-.3 mm Hg and heart rate substantially in anesthetized rabbits. The hypotensive effect was mainly attributable to Enalapril because HDTI by itself had no significant cardiovascular actions **blood pressure** before and after treatment with HDTI was 41.+-.6 mm Hg and 39.+-.3 mm Hg, respectively, n=6 . In the group treated with Enalapril only, **blood pressure** before and after treatment was 54.+-.7 mm Hg and 29.+-.4 mm Hg respectively P . 5, n=5, a decrease of 25.+-.9. . . . A combination of hexamethonium and hydralazine, which act by a different mechanism than Enalapril; i.e., by non-specific vasodilation, also lowered **blood pressure** to a similar extent to that observed for HDTD and Enalapril Table II . However, there is no evidence for synergism. . . .